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09/012,369	01/23/98	MARGOLIS B	231/198

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HM12/1016

EXAMINER	
HUNT, J	
ART UNIT	**PAPER NUMBER**
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/012,369	Applicant(s) Marglis et al.
	Examiner Jennifer Nichols, Nee Hunt	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12 and 19-25* is/are pending in the application.

Of the above, claim(s) *5-9, 11, 12, and 19* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 10, and 20-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

The text of those sections of Tittle 35, U.S. Code not found in this Office Action can be found in a prior Office Action.

Claims 1-12, and 19-25 are pending in the application. Claims 5-9, 11-12, and 19 have been withdrawn from consideration as being drawn to a non-elected species of invention. The instant claims are examined in light of the election of species of cancers and neoplasms and agents which bind APB domains, and claims 20-25 are examined only in as much as they depend from claim 4. Claims 1-4, 10, and 20-25 are under consideration, to the extent noted above.

Claim Rejections Withdrawn

1. The grounds of rejection of claims 2 and 24 under 35 USC 112 2nd paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention is withdrawn in light of applicant's arguments and amendments thereto.

Claim Rejections Maintained

Claims 1, 3-4, 10, and 20-25 stand rejected under 35 USC 112 2nd paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

2. The grounds of rejection of claim 1, for the vague and indefinite recitation of "disease or disorder in an organism characterized by an abnormality in a signal transduction pathway" is maintained for reasons of record.

Applicant argues that the phrase meets the legal standard for definiteness because the claim, when read in light of the specification is definite. Applicant further argues that the examiner has failed to appreciate the definition of "abnormal", found on page 6, lines 25-29 of the specification. With regard to the recitation of "a signal transduction pathway", applicant argues that the amendments to the claim overcome the rejection. Applicant's arguments filed July 6, 2000 have been fully considered but they are not persuasive.

The definition of "abnormal" in the specification as "[other] than occurring in the general population of healthy organisms" does not render the term definite. It is not clear what organisms would be considered healthy and what would not (for example are disease free cancer survivors considered healthy? Would cancer patients in remission be considered healthy?) Further, as set forth in the previous office action, the definition of abnormality in signal transduction is circular. The definition of "abnormal" set forth in applicants arguments refers to "abnormal level" of interaction which is not the same as the instant abnormality in signal transduction". Further, it is not clear if "one or more signal transduction pathways" refers to one particular pathway or one specific type of pathway

3. The grounds of rejection of claim 1 for the vague and indefinite recitation of interaction is maintained for reasons of record.

Applicant argues that the phrase meets the legal standard for definiteness because the claim, when read in light of the specification is definite. Applicant submits that one would clearly associate "interaction" as used in the claim with "binding". Applicant's arguments filed July 6, 2000 have been fully considered but they are not persuasive.

The term "interaction" is not specifically defined in the specification. Furthermore the term could include or not include any number of possible associations, between molecules. Although one of ordinary skill in the art might "associate" the term with binding, they might associate it or not associate it with any number of other possible activities. Thus, as set forth previously, it is not clear which actions define an "interaction" and which do not. It is suggested that if applicant intends the interaction to be that of "binding", the claims be amended to so indicate.

4. The grounds of rejection of claim 3, for the vague and indefinite recitation of "one or more activities" is maintained for reasons of record.

Applicant argues that the amendments to the claim overcome the rejection. Applicant's arguments filed July 6, 2000 have been fully considered but they are not persuasive.

Applicant has amended the claim to recite "one or more kinase functions". As set forth in the previous office action, with relation to activities, functions are not defined in a way which makes it clear what would be considered a kinase function and what would not.

5. The grounds of rejection of claim 4 for the vague and indefinite recitation of "EGF" as a receptor tyrosine kinase when it is not a receptor is withdrawn in light of applicant's amendments thereto.

6. The grounds of rejection of claims 1-4, 10, and 20-25 under 35 USC 112 first paragraph for lacking an enabling disclosure is maintained for reasons of record, reiterated below for clarity.

As set forth in the previous office action, and summarized herein, enablement is lacking because the disclosure of binding by a region in the N-terminus of shc to autophosphorylated EGFR, HER-2 or TRKA is not sufficient support under 35 USC 112 first paragraph for the claims which are drawn to treatment of cancer or neoplasia by administration of an agent which binds to an APB domain, There is no evidence that the disruption or promotion of shc binding to EGFR, HER-2 or any other APB-receptor interactions results in the predicable remediation of symptoms of cancer. No therapeutic agents are provided with said activity, the region of the EGFR to which APB binds is not provided, and no role of the binding in signal transduction is demonstrated. Further, the specification teaches that the specific physiological role of APB binding is unknown and the instant data, which is based on protein fragment interaction may not be correlative with full length proteins.

Applicant's arguments are summarized below, "lettered" for clarity:

A. Applicant argues that the examiner is more concerned with utility than enablement. Specifically, applicant argues that the "APB domain is a necessary component of an important

pathway and widely implicated in the art with certain cancers", and therefor "everyone in the art will therefor appreciate that disruption of this domain or it's partners will likely disrupt cancers and this relationship can advantageously be used in treatments." Applicant further cites examples of in vitro methods of identifying disrupting agents. Lastly, applicant cites In re Brana and Cross vs. Iiuka as support for the correlation of in vitro results to claims which recite in vivo treatment.

B. Applicant argues that the contention of lack of enablement is "fundamentally at odds with almost 50 pages of detailed materials provided in the specification". Specifically, applicant cites where the specification discloses that the invention is useful for assaying EGFR and HER-2 activity. In numerous places applicant argues that the invention is useful for assays and diagnostics, including page 8, paragraphs 2 and 3, page 9, last paragraph, and page 10, paragraph 1 and 3.

C. Applicant refutes the examiner's position that "the EGFR receptor to which the APB domain of Shc binds is not identified" by citing the suggestion in the specification of a possible APB binding region.

D. Applicant argues specific asserted therapeutic uses cited in the specification (such as in gene therapy) and cites specific guidance in the specification in section entitled "administration".

E. Applicant cites the single working example, which uses in vitro results, and further notes numerous citations which describe interactions between growth factors and signaling molecules, as support for enablement.

F. Applicant cites and argues each Wands factor individually.

Applicant's arguments filed July 6, 2000 have been fully considered but they are not persuasive.

With regard to argument A, the rejection is not a rejection for lack of utility, but rather a rejection for lack of enablement. Therefore arguments which are drawn to establishing that the invention has utility are not commensurate in scope with the rejection. The examples and case law cited by the applicant are all only relevant with regard to utility, and since utility is not in question, the arguments are moot.

Applicant attempts to use the court cases as support that in vitro results are sufficient support for claims which recite in vivo treatment. It is noted that the instant cases do NOT establish that in vitro tests are enabling for claims which recite in vivo treatment.

In re Bana decides that in vivo mouse results provide utility for claims which recite in vivo treatment of humans.

Cross et al. V. Iizuka et al. decides that in vitro results provide utility for claims which recite in vivo treatment.

Neither case addresses the issue of in vitro results used as support for enablement of claims which recite in vivo treatment.

With regard to applicant's arguments pertaining to in vitro correlation with claims which recite in vivo treatment, the claims encompass the experimental and unpredictable field of in vivo therapy for mammals having a neoplasia or cancer. An article by *Dermer (BIO/TECHNOLOGY, Vol 12, page 320, 03/1994)* is cited in order to establish the general state of the art and the level of predictability of in vivo therapy. Dermer teaches that "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells in vivo."

Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to mammal or human therapeutic with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further a therapeutic agent must accomplish several tasks to be effective: it must be delivered into circulation and interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In assays, the agent is in contact with the cells during the entire exposure period, whereas in the case of in vivo therapy, exposure at the target site may be delayed or insufficient. Discussing agents used to treat cancer, *Jain, Science Vol 271, 23 February 1996, pages 1079-1080* states that "Because of their potent effect on

cancer cells in vitro and in some in vivo tumor systems, these agents have been heralded as breakthrough drugs, or "magic bullets" and have been enthusiastically accepted as such by policy makers, investors, and the general public. Although the potential for using these agents in cancer therapy is great and almost certainly justified, clinical results to date have not met the high expectations extrapolated from carefully planned and performed preclinical studies." *Jain , R. K. (Cancer and Metastasis Reviews, 9:753-266, 1990)* teaches that the efficacy in cancer treatment of novel therapeutic agents such as monoclonal antibodies, cytokines and effectors cells has been limited by their inability to reach their target *in vivo* in adequate quantities. Three physiological factors responsible for the poor localization of macromolecules in tumors have been identified: (I) heterogeneous blood supply, (ii) elevated interstitial pressure which lowers fluid extravasation, and (iii) large transport distances in the interstitium. Furthermore, the average vascular surface area decreases with tumor growth, hence reducing transvascular exchange in large tumors compared to smaller tumors. The molecule may also bind non-specifically to proteins or other tissue components; bind specifically to the target and or be metabolized, which further lowers the effective diffusion rate by reducing the amount of mobile molecule. Finally, although the effector cells are capable of active migration, peculiarities of the tumor vasculature and interstitium may be also responsible for poor delivery.

Therefore one of skill in the art would conclude that in vivo therapy of cancer is an unpredictable and complex art and that in vitro tests are not sufficient to enable in vivo treatments.

With regard to argument number 2, applicant cites numerous examples in the specification where the instant invention is used for assays and diagnostics. These examples are not commensurate in scope with the claims, which are drawn to methods of in vivo treatment. As set forth, the field of in vivo cancer therapy is complex and unpredictable and therefore examples which describe assays and diagnostics are not enabling for claims which recite in vivo therapy.

With regard to argument number 3, applicant has cited in the disclosure the description of an APB region, however the asserted APB binding region does not provide a specific sequence, but rather a "preferred" example of what the domain "can be", and includes only 3 known amino acids for a polypeptide agent which can contain any number of amino acids. Although this provides limited guidance as to what would be considered an APB region, it does not provide the sequence as it is asserted by applicant.

With regard to argument number 4, although applicant cites suggestions for use of the compound in therapy, applicant has provided no evidence that the compound would be effective for in vivo therapy. As set forth above, in vivo therapy is unpredictable and thus the mere assertion of effectiveness in vivo is insufficient support to enable claims which recite in vivo therapy.

With regard to argument number 5, the solitary working example cited by applicant is an in vitro example and not correlative to in vivo therapy as set forth above.

With regard to the Wands factors, set forth in argument number 6, applicants arguments are addressed below:

Quantity of Experimentation Necessary/Amount of Guidance Presented:

Applicant argues that the "details of the specification comport well with this exposition of the law", referring to the citation of numerous court cases which discuss the quantity of experimentation necessary. As set forth above, the field of in vivo cancer therapy is highly unpredictable and complex and in vitro test data is not generally correlative with in vivo claims.

The presence or absence of working examples:

As set forth above, applicant's disclosure contains a single in vitro working example which is insufficient to enable claims which are drawn to the unpredictable field of in vivo cancer treatment.

The Nature of the Invention:

Applicant asserts that the "nature of the invention" is a domain in the amino terminus of Shc, however the claims are drawn to treatment of cancer (which is unpredictable as set forth above) using any protein with an APB binding domain. This is not predictable, and is a broadly claimed invention, and thus the nature of the invention would not necessarily be effective using "methodologies well known in the art" as asserted by applicant.

The State of the Prior Art and the Relative Skill of Those in The Art:

Applicant sets forth that signal transduction is implicated in cancer and neoplasms, supported by "literally dozens of citations". Applicant further discusses that the APB binding domain may be

used "advantageously and in unprecedented fashion"to modify these systems. Applicant further sets forth general teaching references to support "pharmaceutical formulations" and "how to produce targeting molecules", however applicant's arguments are not commensurate in scope with the claims, and therefor fails to address the issue of the state of the prior art and the skill of those in the art as it pertains to in vivo therapy of cancer. As set forth above, the art of cancer therapy is highly complex.

Predictability or Unpredictability:

Applicant reiterates the cited examples, which as set forth above do not pertain to in vivo cancer therapy. Applicant further submits that the amount of knowledge in the art is sufficient to render the art predictable, however as set forth above, the knowledge in the art is that the art itself is unpredictable.

The Breadth of the Claims:

Applicant asserts that the claims are tailored to comport with the amount of specification guidance, but as set forth above, the guidance and skill in the art is insufficient to enable claims which recite in vivo cancer therapy.

Regarding examiner's notation of evidence in the specification which demonstrate lack of enablement, applicant argues that the specification must be considered in context, but has not argued these grounds of rejections.

In summary, applicant's arguments assert but do not support the contention that a single in vitro result is enabling for claims which recite in vivo therapy. Further applicant cites numerous references and examples which are drawn either to in vitro tests, mere speculation, or the compound itself, not the claimed invention, which is specifically in vivo cancer therapy. Therefore one of ordinary skill in the art would not be enabled to practice the inventions, as set forth in the previous office action.

New Grounds of Rejection

7. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The new limitation "at least one" signal transduction pathways" is not supported by the disclosure and claims as originally filed.

No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Nichols, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Nichols, Nee Hunt

September 27, 2000

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